Remarks

The present invention provides three-dimensional spatial representations of exemplary isolated polyketide synthases (e.g., chalcone, stilbene, or pyrone synthase) with defined coordinants comprising at least fourteen active site alpha-carbon atoms thereof. The present invention embraces the discovery by the Applicants of the first three-dimensional structure of a chalcone synthase reported in the scientific literature. Thus, the present invention also provides crystalline polyketide synthases. The invention crystalline materials and three-dimensional representation thereof have great utility in the understanding of polyketide catalysis and the design of mutant polyketide synthases. Further, the present invention provides methods for designing mutant polyketide synthases, for predicting the activity and/or substrate specificity of putative naturally occurring and mutant polyketide synthases, and for identifying polyketide synthase substrates and/or inhibitors.

By the present communcation, Claims 1 and 22 have been amended to define Applicants' invention with greater particularity. No new matter is introduced by the subject amendments as the amended claim language is fully supported by the specification and original claims. Specifically, support for the amendment to Claim 1 is found, for example, in the specification at page 2, paragraph 2. Furthermore, the amendment to Claim 22 merely corrects an inadvertent typographical error.

Claims 1-39 are pending, with claims 1, 6, 17, and 22-26 currently under consideration, and claims 2-5, 7-16, 18-21, and 27-39 withdrawn from consideration as being drawn to non-elected inventions or species. A detailed listing of all claims, that are, or were, in the application, irrespective of whether the claims(s) remain under examination, is presented in the **Listing of Claims**, beginning on page 7 of this communication, with an appropriate status identifier for each claim.

By the present communication, the specification has been amended to correct an inadvertant typographical error at page 9, line 11, wherein PDB Acc. No. 1K6I is incorrectly recited, rather than the proper PDB Acc. No. 1D6I. Correction of this inadvertant typographical error introduces no new matter (note the express recitation of PDB Acc. No. 1D6I in Claim 6 as originally filed.) The fact that recitation of 1K6I is incorrect would be immediately clear to those of skill in the art due to the recognition that PDB Acc. No. 1K6I describes the crystal structure of Nmra, which is a negative transcriptional regulator. Further, the recitation of 1D6I in the specification is correct (as opposed to amendment of claim 6) since PDB Acc. Nos. 1BI5, 1D6F, 1D6I, and 1D6H share a single common authorship, and all relate to chalcone synthase and derivatives thereof.

By the present communication, the specification has been amended as requested by the Examiner to address the following items:

First, in response to the Examiner's objection to the title as allegedly not being descriptive (Office Action, page 5, paragraph 6), the title has been changed to "Three-Dimensional Structure of Polyketide Synthases."

Further, reference to trademark terms (in the paragraph beginning on page 173, line 3) has been amended as requested by the Examiner (Office Action, page 5, paragraph 6 to page 5, paragraph 1).

Further, all references to possible embedded hyperlinks (Office Action, page 5, paragraph 2) have been removed in the paragraphs beginning on page 15, line 8, page 6, line 22, page 17, line 17, and page 9, line 5.

Finally, the objection to the incorporation by reference of allegedly essential matter (Office Action, page 5, paragraph 3) wherein the reference is not a U.S. patent, U.S. patent application publication, or a pending U.S. application (MPEP 608.01), has been rendered moot by the present amendment to the specification. Accordingly, PDB Acc. Nos. 1BI5, 1D6F, 1D6I,

and 1D6H have been literally incorporated into the specification as new Tables 5-8, respectively. No new matter is introduced by the subject amendment, permitted by MPEP 608.01(p)(I)(A)(2), as the contents of these PDB accession numbers were incorporated by reference in their entireties in the specification as originally filed (page 9, lines 5-14). Due to length exceeding 50 pages, each of Tables 5-8 have been incorporated by reference under 37 C.F.R. § 1.52(e)(1)(iii) to files "Table5.txt", "Table6.txt", "Table7.txt", and "Table8.txt", respectively, of CD-R disk "Tab-5-8", two copies of which are provided herewith. Entry of CD-R disk "Tab-5-8" is respectfully requested.

Accordingly, in view of the amendments to the specification discussed herein, reconsideration and withdrawal of the objections discussed above are respectfully requested.

The restriction of claims 1-39 under U.S.C. § 121 and § 372 as allegedly being drawn to five separate inventions is respectfully traversed. It is respectfully submitted that the claims have been restricted into an excessive number of groups. For example, Applicants submit that the claims of Groups III-V (i.e., claims 12-16 and 28-39) form a group with unity of invention, wherein the "special technical feature" required for such unity of invention is the disclosed three-dimensional X-ray crystallographic structure of an isolated polyketide synthase with defined structural coordinates for at least 14 active site alpha-carbon atoms. Accordingly, reconsideration and withdrawal of the requirement for restriction are respectfully requested. Alternatively, regrouping of the claims into fewer groups is requested.

However, in order to be fully responsive, Applicants hereby affirm the election of the claims of Group I (i.e., claims 1-6, and 17-27) for prosecution on the merits.

The requirement for election of species under PCT Rules 13.1 and 13.2 is respectfully traversed. It is respectfully submitted that the specific identity of the side chains at positions 163, 303, 336, and 215, as recited by the Examiner (Office Action, page 2, last paragraph), are not required by the invention as claimed. See, for example, Claim 1 which is drawn to a three-

dimensional spatial representation of an isolated polyketide synthase having at least 14 active site alpha-carbons having the structural coordinates of Table 1. Accordingly, the three-dimensional spatial representation of the invention does not require the identification or three-dimension coordinates of atoms which are not alpha-carbon atoms, and in particular does not require such information of any side chain atoms.

However, in order to be fully responsive, Applicants hereby affirm the election of the first species of claim 6 having designation 1BI5 for prosecution on the merits.

The rejection of Claims 1, 17 and 22-26 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the claims allegedly contain subject matter "which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, page 6, paragraph 1).

Specifically, Applicants respectfully disagree with the Examiner's assertion that Claims 1 and 17 are allegedly "directed to all possible polyketide synthases from any biological source, which comprises an active site comprising 14 active site α-carbons having the atomic coordinates in Table 1" (Office Action, page 6, paragraph 2).

Contrary to the Examiner's assertion, Claim 1, as amended, is drawn to a three-dimensional representation of specific polyketide synthases (i.e., chalcone, stilbene, or pyrone synthase) wherein the three-dimensional representation is defined by the three-dimensional coordinates of at least 14 active site alpha-carbon atoms. Detailed examples of the mutagenesis, expression, purification, crystallization, data collection, data processing, structure determination, model building, model refinement, and structure description of chalcone synthase, stilbene synthase, and pyrone synthase are provided in the specification (pp. 175-193). Accordingly, it is respectfully submitted that Claims 1 and 17 (which depends from Claim 1) are fully described,

and that Applicants were in possession of the invention as claimed at the time of filing, in compliance with 35 U.S.C. § 112, first paragraph.

The rejection of Claims 1, 17, and 22-26 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement (Office Action, page 6, paragraph 3) is respectfully traversed. This rejection is based on an erroneous evaluation of the Wands factors by the Examiner, as follows:

1) The nature of the invention

The Examiner has incorrectly characterized the invention, which is drawn specifically to a three-dimensional representation of an isolated polyketide synthase, wherein the representation is defined by the three-dimensional coordinates of at least 14 active site alpha-carbon atoms. Thus, the invention, as defined by Claim 1, is defined both structurally (with reference to three-dimensional coordinates of at least 14 active site alpha-carbon atoms in Table 1) and functionally (with reference to chalcone, stilbene, and pyrone synthases).

2) The state of the prior art

There is no acknowledgement in the Office Action that Applicants were the first to obtain an X-ray crystallographic structure of a polyketide synthase such as chalcone synthase. Indeed, the ability to obtain such crystal structures was a profound contribution to the body of scientific knowledge, forming the basis for the invention embraced by the current claims.

3) The relative skill of those in the art

The relative skill of those in the relevant art is extremely high.

4) The predictability or unpredictability of the art

Applicants submit that the predictability in the art of X-ray crystallography was increased significantly with respect to polyketide synthases by the Applicants' own work leading to the subject invention due to Applicants' disclosure of conditions for expression, purification, crystallization, data collection, data analysis, and model building for the first structure of chalcone synthase reported in the literature. Furthermore, as known by those of skill in the art,

the screening of conditions for obtaining suitable crystals for X-ray diffraction is routine, being conducted according to methodologies known since the 1980's (e.g., A. MacPherson, Protein Crystallization, 1982, John Wiley and Sons, Inc. New York). Furthermore, the present invention, as defined, for example, by Claim 1, provides for the three-dimensional spatial representation of a defined poplyketide synthase, wherein the synthase is chalcone, stilbene, or pyrone synthase. Accordingly, it is respectfully submitted that the assertions by the Examiner on the low predictability involved in determining the crystallization conditions necessary therefor (Office Action, page 7, line 34) are immaterial in view of the defined nature of the polyketide synthase embraced by Claim 1.

5) The breadth of the claims

It is respectfully submitted that the claims of the present invention, as currently amended, are of a breadth which is fully supported by the specification. Specifically, Claim 1 embraces a three-dimensional spatial representation of defined polyketide synthases, wherein the three-dimensional spatial representation comprises at least fourteen active site alpha-carbons having the structural coordinates of Table 1.

6) The amount of direction and guidance presented

As acknowledged by the Examiner (Office Action, page 6, paragraph 4 continuing onto page 7), the specification provides guidance and examples of the preparation and crystallization of exemplary polyketide synthases, chalcone synthase and stilbene synthase. Additionally, the specification includes the three-dimensional X-ray crystallographic structure of pyrone synthase (pp. 23-147). It is respectfully submitted that the amount of direction or guidance provided by the present specification is commensurate in scope with the claims, as amended.

7) The presence or absence of working examples

The present claims are supported by extremely detailed examples, in the form of X-ray crystallographic coordinates, for exemplary polyketide synthases, chalcone synthase and pyrone synthase.

8) The quantity of experimentation necessary

Based on the substantial guidance provided by the specification, and the well developed state of the relevant art, the experimentation required by the present invention is not undue. Accordingly, Applicants respectfully disagree with the Examiner's assertion

> ... that one skilled in the art would require additional guidance, such as information regarding the gene encoding said synthase, the amino acid sequences of the chalcone/polyketide synthase, and identify a crystallization conditions that produce a crystal suitable for structure determination by X-ray crystallography. Without such guidance, the experimentation left to those skilled in the art is undue.

(Office Action, page 7, last sentence of top paragraph). The Examiner's concern with the quantity of experimentation required to practice the present invention is respectfully submitted to be misplaced as the quantity of experimentation is only one factor involved in determining whether undue experimentation is required; moreover, time and difficulty of experiments are not determinative if they are merely routine (MPEP § 2164.06).

Accordingly, reconsideration and withdrawal of the rejection of Claims 1, 17, and 22-26 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully requested.

The rejection of claims 1, 6, 17, 22, and 26 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention is respectfully traversed. Following the format of this rejection provided by the Examiner (Office Action, page 8, paragraphs 1-6) specific comments with respect to each of these claims follow:

(a) Claim 6: By the present communication, PDB Acc. No. 1BI5 has been incorporated into the specification as permitted by MPEP 608.01(p).

(b) Claim 1: Contrary to the Examiner's assertion, it is respectfully submitted that Claim 1 is not indefinite and confusing. Indeed, for examination purposes, the Examiner was readily able to surmise that reference was to residues of SEQ ID NO:1. Thus, for further clarification, by the present communication, the amino acid residues of Table 1 have been further identifed by reference to SEQ ID NO:1.

(c) Claim 22: The Examiner's observation of an obvious typographical error (comprising two periods in claim 22) is acknowledged. Accordingly, by the present communication, Claim 22 has been amended to delete the final period.

(d) Claim 26: The Examiner's assertion that Claim 26 is allegedly indefinite reflects a misreading of the claim as witnessed by the Examiner's assertion that

> The clause "the chalcone synthase is selected from the group consisting of chalcone....." in claim 26 renders the claims indefinite ...

(Office Action, page 8, paragraph 5). In contrast to the Examiner's truncated reading of the claim, Claim 26 **in full** recites (emphasis added):

> The crystalline complex of claim 23, wherein the chalcone synthase **substrate** is selected from the group consisting of chalcone, naringenin, resveratrol, cerulenin, acyl-CoA, malonyl-CoA, and hexanoyl-CoA.

Accordingly, the term "**substrate**" found in Claim 26 is missing in the Examiner's comments reproduced above. It is well known in the art of enzymology and enzyme nomenclature that the name ascribed to an enzyme does not necessarily reflect the direction of chemical reaction or even the reactants involved in the reaction. Furthermore, Applicants disagree with the Examiner's statement that "An enzyme named chalcone synthase should produce chalcone as a product." (Office Action, page 8, paragraph 5). Indeed, as well known to those of skill in the art, enzymes, including polyketide synthases, can be promiscuous in both the forward and reverse directions of catalysis.

(e) Claim 17: As discussed above under point (b), Claim 1, from which claim 17 depends, has been amended.

Accordingly, reconsideration and removal of the rejection of Claims 1, 6, 17, 22, and 26 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

The rejection of Claims 1 and 6 under 35 U.S.C. § 102(a) as allegedly being anticipated by PDB Acc. No. 1BI5 is respectfully traversed. PDB Acc. No. 1BI5 is Applicants' own work. Inventors of the current application as filed are Noel, Ferrer, Jez, Austin, and Bowman. Authors of PDB Acc. No. 1BI5 are Ferrer, Jez, Bowman, Dixon, and Noel. Accordingly, the contributions of author Dixon and inventor Austin must be reconciled.

Specifically, author Dixon did not contribute to the presently claimed invention. Applicants are prepared to provide a declaration [In re Katz, 687 F .2d 450, 215 USPG 14 (CCPA 1982)] under 37 C.F.R. § 1.132 attesting to this fact. With respect to inventor Austin, due to the withdrawal of claims to which inventor Austin contributed, Austin is not an inventor of the presently claimed invention. Applicants will provide a petition to remove Austin as an inventor; however, Applicants defer formal correction of inventorship at this time pending final resolution of the elected claims and the possible rejoinder of currently non-elected claims.

Accordingly, publication of PDB Acc. No. 1BI5 is not a publication by an "other," and PDB Acc. No. 1BI5 is, therefore, not available as prior art against the present claims. Thus, reconsideration and removal of the rejection of Claims 1 and 6 are respectfully requested.

The rejection of Claims 1 and 6 under 35 U.S.C. § 102(b) as allegedly being anticipated by Junghans *et al.* (*Plant Mol. Biol.* **22**, 239-253, 1993) is respectfully traversed. Specifically, Applicants' invention, as defined, for example, by Claim 1, distinguishes over Jurghans *et al.* by requiring a three-dimensional spatial representation of an isolated polyketide synthase with defined coordinants comprising at least 14 active site alpha-carbon atoms as set forth in Table 1. In contrast, Junghans *et al.* does not teach the three-dimensional structure of any compound.

Junghans *et al.*, therefore, does not anticipate either claim 1 or claim 6. Accordingly, reconsideration and removal of the rejection of Claims 1 and 6 are respectfully requested.

In view of the above amendments and remarks, favorable reconsideration of the application is respectfully requested. In the event that any issues remain to be resolved concerning the present application, the Examiner is encouraged to contact the undersigned by telephone so that a prompt resolution may be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date September 26, 2005

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Enclosure: CD-R "Tab-5-8" (2 copies)